REMARKS

By this preliminary amendment, Applicant has canceled claims 24 and 28-36. New claims 37-46 have been added. Support for these claims is found throughout the specification as discussed hereinafter. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 37-46 are before the Examiner. Favorable consideration of these claims is respectfully requested.

Rejection of claims 24, 28-30 and 35 under 35 U.S.C. 112, first paragraph

Examiner rejected the above-identified claims under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention or to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicant had argued that the above-identified claims should be allowed because they closely followed the structure of previously granted claims, except for conservative substitutions of functional language at the exact points where this was necessary for fully claiming the invention disclosed in the specification. Although aware that each application is examined on its own merits, Applicant felt that he might be able to facilitate the Examiner's work in this case, in which text, claim portions alluded to, Art Unit and Examiner are identical.

Cancellation of the above-identified claims renders the rejection moot. However, anticipating that newly added claims may be rejected on similar grounds, Applicant would like to comment on the grounds for rejection advanced by the Office. Examiner wrote in the second paragraph on page 3 of the most recent Office Action "Applicants have only described their invention based on function, yet the correlation between structure and function is not known. The specification does not provide any guidance on how to predictably manipulate (how to make and use) or mutate undiscovered and undisclosed transcription factors so that they will stay in the active form once stimulated. Thus the artisan would not have been unable to have prepared the claimed nucleic acid [molecular circuit] without undue experimentation...." Applicant does not recognize his

invention in this paragraph. His invention relates to molecular circuits that constitute novel assemblies of available factors/nucleic acids and not to the description of novel transcription factors. The molecular circuits of the invention only make use of suitable transcription factors. Examples of such suitable transcription factors (of which several were disclosed in the prior art by the inventor and others) were provided in the specification to illustrate the invention. Furthermore, the invention does not relate to transcription factors mutated so that they will stay in the active form once stimulated. The inventive molecular circuitry includes an element of feed-forward regulation that provides for sustained transcription and translation of transcription factor genes upon activation but not for a change in the activity status of the transcription factors themselves. Hence, the argument made by the Examiner does not apply to the invention described in the application as filed.

In the second paragraph on page 2 Examiner wrote "Applicants have only described their invention based on function, yet the correlation between structure and function is not known. The claims encompass a genus of nucleic acids defined only by their function wherein the relationship between the structural features of members of the genus and said function have not been defined. In the absence of such a relationship either disclosed in the as filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition. The fact that one could have assayed a nucleic acids of interest does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (other than those that might particularly disclosed in an application) would fall within the scope of what is claimed. It would require undue experimentation (be an undue burden) to randomly screen undefined nucleic acids for the claimed activity." To the extent that this rejection language refers to transcription factor genes, it does not relate to the invention as described and claimed (see the previous paragraph).

New claim 37 reads as follows:

> "An isolated nucleic acid delivered into a cell comprising a gene for a transcription factor that is operably linked to a nucleotide sequence with which it is not normally associated that directs the transcription of the gene such that the rate of transcription increases in response to a stress and in response to the transcription factor."

Support for this claim that describes one of the two elements of a two-element molecular circuit of the invention is found, e.g., on page 3, lines 5-7:

"...a first nucleic acid molecule that comprises a gene encoding a transcription factor and a first promoter activatable by stress and by the transcription factor, wherein the first promoter and the transcription factor gene are operably linked,..."

The same composition is also described on page 3, lines 18-21, page 4, lines 2-4 and lines 16-18, page 12, lines 6-7 (example of a type 1 circuit, and page 21, lines 3-6 (example of a type 2 circuit) and lines 19-21 (example of a type 3 circuit).

Components of molecular circuits are delivered into a cell. Support for this contention can be found throughout the specification, e.g., page12, lines 10-12, page 13, lines 19-25, page 23, lines 17-21, page 26, lines 3-6, page 29, line 27 – page 30, line 26, and examples 1 and 2. Because the limitation "delivered into a cell" is not given patentable weight in a product claim, Applicant introduced the term "isolated nucleic acid" in the definition of the product to indicate that the product in question exists outside of the cell, i.e., is not part of the normal genome of a cell. The term "isolated nucleic acid molecule" is also defined on page 8, lines 4-9.

In claim 37 and subsequent claims the term "promoter" that appears in the description of the element on page 3, lines 5-7, and elsewhere was replaced with language appearing in the definition of the term "promoter" that is found on page 8, lines 16-21:

"A promoter is a nucleotide sequence that directs the transcription of a structural gene...If a promoter is an inducible promoter, then the rate of transcription increases in response to an inducing agent..." A structural gene is a gene encoding a protein (page 10, lines 9-11).

This definition intentionally had been written broader than certain definitions that might be found in "the dictionary" (textbooks) in order to capture equivalents of promoters disclosed specifically in the specification, which equivalents are obvious to the inventor and will be obvious to anyone skilled in the art. Because doubt remains about whether the courts have finally resolved the question as to whether a term appearing in a claim is to be interpreted by reference to "the dictionary" or by reference to the specification, prudent practice requires that any definition that might differ from the dictionary definition be directly written into a claim. It is noted that construction of promoters responsive to a transcription factor is a well-defined art since the 1980s. (A protein is only rightfully labeled a "transcription factor" if a target gene and, typically, the specific nucleic acid sequence bound by the protein are known.) What a stress-responsive promoter is and/or how it can be constructed is explained in the paragraph bridging pages 14 and 15. An example for the construction of a promoter responsive to a transcription factor is provided on page 19, lines 21-24. Finally, an illustrative example of a promoter that is responsive to a stress as well as responsive to a transcription factor (a chimeric factor comprising a LexA DNA binding domain) is found on page 19, lines 24-30 and page 20, lines 1-2. The term "operably linked" is standard (see also the definition on page 10, lines 24-26).

The limiting term "with which it is not normally associated" was included to clearly distinguish the composition of claim 37 from one described in a reference newly cited by the Examiner (see below). Support for the limitation is found on page 11, lines 1-3:

"In recombinant constructs described below, a regulatory element or a promoter controls the expression of a gene which is not associated with the regulatory element or promoter in nature..."

Further support is found throughout the specification as none of the many molecular circuits and components thereof described contains a gene that is linked to its normal promoter.

New claim 38 reads as follows:

> "An isolated molecular circuit delivered into a cell, comprising (a) a gene encoding a transcription factor, the gene encoding the transcription factor being operably linked to a nucleotide sequence with which it is not normally associated that directs the transcription of the gene such that the rate of transcription increases in response to a stress and in response to the transcription factor, and (b) a gene of interest, the gene of interest being operably linked to a nucleotide sequence with which it is not normally associated that directs the transcription of the gene of interest such that the rate of transcription increases in response to the transcription factor."

Support for claim 38 that describes a two-element molecular circuit of the invention is found, e.g., on page 3, lines 4-10:

"...molecular circuits comprising (a) a first nucleic acid molecule that comprises a gene encoding a transcription factor and a first promoter activatable by stress and by the transcription factor, wherein the first promoter and the transcription factor gene are operably linked, and (b) a second nucleic acid molecule that comprises a gene of interest and a second promoter activatable by the transcription factor, wherein the second promoter and the gene of interest are operably linked."

For further support see also page 3, lines 14-17, and under claim 37 above. Claim 40 describes a variant of the molecular circuit of claim 38. Specific support for claim 40 is found on page 3, lines 10-14:

"In a variation of this type of molecular circuit, the molecular circuit comprises a gene of interest that encodes a transactivator, and the molecular circuit further comprises a nucleic acid molecule comprising a second gene of interest and a promoter activatable by the transactivator, wherein the second gene of interest and the transactivatable promoter are operably linked."

"Transactivator" is a transcription factor as is explained on page 9, lines 1-2. For further support, see page 23, lines 1-6.

New claim 43 reads as follows:

> "An isolated molecular circuit delivered into a cell, comprising (a) a gene encoding a first transcription factor, the gene encoding the first transcription factor being operably linked to a nucleotide sequence with which it is not normally associated that directs the transcription of the gene such that the rate of transcription increases in response to a stress, (b) a gene encoding a second transcription factor, the gene encoding the second transcription factor being operably linked to a nucleotide sequence with which it is not normally associated that directs the transcription of the gene encoding the second transcription factor such that the rate of transcription increases in response to the first transcription factor and in response to the second transcription factor, and (c) a gene of interest, the gene of interest being operably linked to a nucleotide sequence with which it is not normally associated that directs the transcription of the gene of interest such that the rate of transcription increases in response to the second transcription factor, whereby the first and second transcription factors may be identical molecules."

For support, see under claims 37 and 39. Specific support can be found on page 4, lines 1-10:

"...molecular circuits comprising (a) a first nucleic acid molecule that comprises s gene encoding a first transcription factor and a first promoter actvatable by stress, wherein the first promoter and the first transcription factor are operably linked, (b) a second nucleic acid comprising a gene encoding a second transcription factor and a second promoter activatable by the first transcription factor and the second transcription factor, wherein the second promoter and the second transcription factor gene are operably linked, and (c) a third nucleic acid molecule that comprises a gene of interest and a third promoter activatable by the second transcription factor, wherein the third promoter and the gene of interest are operably linked."

The following sentence (page 4, lines 10-14) explains that the latter nucleic acids can be separate or combined: "These molecular circuits may comprise (a) three separate nucleic acid molecules, (b) the third nucleic acid molecule and a single nucleic acid molecule that comprises the first nucleic acid molecule and the second nucleic acid molecule, or (c) a single nucleic acid comprises the first nucleic acid molecule, the second nucleic acid molecule, and the third nucleic acid molecule."

If the first and second transcription factor genes are identical, the molecular circuit of claim 43 becomes identical with the circuit described on page 3, lines 18-26: "...molecular circuits comprising (a) a fist nucleic acid molecule that comprises a gene encoding a transcription factor and a first promoter activatable by stress, wherein the first promoter and transcription factor are operably linked, (b) a second nucleic acid comprising a gene encoding the transcription factor and a second promoter activatable by the transcription factor, wherein the second promoter and the transcription factor gene are operably linked, and (c) a third nucleic acid molecule that comprises a gene of interest and a third promoter activatable by the transcription factor, wherein the third promoter and the gene of interest are operably linked."

That the elements of the latter circuit can be administered separately or combined in different ways is indicated by the following sentence (page 3, lines 26-30).

New claim 42 reads as follows:

> "An isolated nucleic acid or set of nucleic acids delivered into a cell comprising (a) a gene encoding a first transcription factor, the gene encoding the first transcription factor being operably linked to a nucleotide sequence with which it is not normally associated that directs the transcription of the gene such that the rate of transcription increases in response to a stress, and (b) a gene encoding a second transcription factor, the gene encoding the second transcription factor being operably linked to a nucleotide sequence with which it is not normally associated that directs the transcription of the gene encoding the second transcription factor such that the rate of transcription increases in response to the first transcription factor and in response to the second transcription factor, whereby first and second transcription factor may be identical molecules."

This claim captures the first two elements of the molecular circuits of claim 43.

New dependent claim 39 reads as follows:

> "The molecular circuit of claim 38, wherein the gene encoding a transcription factor is selected from the group consisting of a gene for a mutated heat shock transcription factor, a chimeric transcription factor, a constitutively active transcription factor and a transcription factor active in the presence of a second stimulus other than a stress."

Support for the elements present in this claim and in analogous dependent claims 41 and 44 can be found in the specification. For "mutated heat shock transcription factor" see p.12, lines 8, 14 and 16, and p.14, lines 14 and 17. For "chimeric transcription factor" see the definition on p.9, lines 3-6, and the examples on p.19, lines 15-20, p.20, lines 21-28

(The factors discussed are specifically called "chimeras" on line 27.), and p.21, lines 21-23. For "constitutively active transcription factor" see p.21, lines 17-18. For "a transcription factor active in the presence of a second stimulus other than a stress" see the example of p.22, lines 4-9 and line 20. For the characterization of the second stimulus as being different from a stress see the sentence bridging pp. 21 and 22.

New claim 45: "A recombinant eukaryotic host cell comprising a molecular circuit according to any of claims 38-41, 43 and 44".

Support for this claim is found on page 5, lines 3-6: "The present invention also contemplates recombinant host cells that comprise a molecular circuit. The molecular circuit may have the form of a single expression vector or an expression vector set, as described above. Suitable eukaryotic host cells include insect cells, avian cells, yeast cells, and mammalian cells."

New claim 46: "A recombinant virus or a set of recombinant viruses comprising a molecular circuit according to any of claim 38-41, 43 and 44".

Support for this claim is found on page 5, lines 13-15: "The present invention also contemplates viruses that comprise an expression vector system described above. Suitable viruses include adeno-associated viruses, adenoviruses, *Herpes simplex* viruses, alphaviruses and pox viruses." See also the section entitled "Use of a Stress-Inducible Circuit for Gene Therapy" beginning on page 25.

Objections to claims 31-34 and 36 under 37 CFR 1.75(c)

The claims mentioned were inadvertently made multiply dependent on multiply dependent claims. The objections are moot due to the cancellation of all claims concerned.

Rejection of claims 24 and 28 under 35 USC 102(b)

Claims 24 and 28 were rejected as being anticipated by Wu and Newton. 1997. J. Bacteriol. 179, 514-521. Although cancellation of the claims concerned renders the rejection moot, Applicant wishes to discuss the grounds for rejection advanced by the Office and explain why the newly proposed claims are not anticipated by the cited art. The Wu and Newton article described a Caulobacter rpoH gene and associated promoters P1 and P2. Experimental evidence was interpreted as indicating that promoter P2 is stimulated by sigma32, the product of the rpoH gene. The Examiner considered a nucleic acid comprising the rpoH promoter P2 and the rpoH gene to be equivalent to the composition of claim 24 that comprises a gene for a transcription factor operably linked to a promoter activatable by a stress and the transcription factor when the transcription factor gene in the claim is substituted by the rpoH gene. By postulating that the gene of interest of claim 28 could also encode sigma32, Examiner similarly rejected this claim as being anticipated by the Wu and Newton reference. Examiner's argument requires that sigma32, a prokaryotic RNA polymerase co-factor, be re-classified as a transcription factor. Applicant believes that such re-classification would be difficult to justify on mechanistic grounds and would only give rise to unnecessary confusion, considering that eubacteria actually contain transcription factors that have attributes closely resembling those of eukaryotic transcription factors (the transcription factors the instant invention is concerned with). Regarding the rejection of claim 28, it is correct that "the limitation of "gene of interest" does not indicate that this gene needs to be a heterologous gene or cannot be the gene for the transcription factor itself". (The transcription factor gene being the Caulobacter rpoH gene.) However, "the gene of interest" is defined specifically on page 11, lines 24-25 as "an RNA polymerase II gene encoding an RNA product or a polypeptide product". As RNA polymerase II and, consequently, RNA polymerase II genes are not found in eubacteria, the "gene of interest" in claim 28 cannot be substituted with a Caulobacter rpoH gene.

Applicant would like to point out an even more fundamental difference between the Wu and Newton composition and the elements of the molecular circuits described by the instant application: the Wu and Newton composition relates to a gene that is functionally

linked to its normal regulatory/promoter sequences. By contrast, as is specifically indicated in the specification on page 11, lines 1-3, the constructs of the invention relate to genes linked to regulatory/promoter sequences with which they are not associated in nature. This limitation was introduced into the new claims to positively distinguish them from Wu and Newton.

Applicant previously filed a terminal disclaimer to obviate a double patenting rejection in the instant case (01/20/2004). In view of the foregoing remarks and amendments in the claims, Applicant believes that the claims currently before the Examiner are in condition for allowance, and notice of such action is respectfully requested. Examiner is cordially invited to call Applicant at 41-21-728-0320 if clarification is needed or if Examiner believes a telephone interview would facilitate the prosecution of the subject application.

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Respectfully Submitted,

Richard Voellmy, Applicant & Attorney
Reg. No. 40,859

*Avenue des Cerisiers 39 B
CH-1009 Pully
Switzerland

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